AD_____

Award Number DAMD17-94-J-4027

TITLE: Predoctoral Training in Breast Cancer Detection and Treatment

PRINCIPAL INVESTIGATOR: John S. Leigh, Jr., Ph.D.

CONTRACTING ORGANIZATION: University of Pennsylvania
Philadelphia, Pennsylvania 19104-3264

REPORT DATE: August 1999

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY *(Leave blank)*	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1999	Final (1 Aug 94 - 31 Jul 99)

4. TITLE AND SUBTITLE
Predoctoral Training in Breast Cancer Detection and Treatment

5. FUNDING NUMBERS
DAMD17-94-J-4027

6. AUTHOR(S)
John S. Leigh, Jr., Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Pennsylvania
Philadelphia, Pennsylvania 19104-3264

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*

Our training program in the detection and treatment of breast cancer has provided an excellent training opportunity to those interested in pursuing research careers in this interdisciplinary area. We have structured our program so that each of the four predoctoral trainees were assigned dual advisors. Each trainee was supervised by a well trained basic scientists as well as a clinician. In addition, each trainee attended weekly journal club meetings and monthly seminars. The field of research encompassed a wide variety of disciplines including Genetics, Biophysics, Biochemistry, Physiology, Tumor Biology, Electrical Engineering, and Computer Science as well as many clinical fields (including Surgery, Radiology, Oncology, Radiation Therapy).

The University of Pennsylvania has developed a unique broadly based interdisciplinary program of graduate education aimed at applying physical principles to the clinical problems inherent in the detection and treatment of breast cancer. During the past year our main research effort was aimed at improving the detection and treatment of breast cancer. This effort involved many aspects of detection both by imaging breast cancers as well as genetic screening. We began the development of improved treatment protocols based on increased knowledge of the metabolism of breast disease.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
18

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

____ Where copyrighted material is quoted, permission has been obtained to use such material.

____ Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

____ Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

JSL In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and use of Laboratory Animals of the Institute of Laboratory Resources, national Research Council (NIH Publication No. 86-23, Revised 1985).

JSL For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

____ In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

____ In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

____ In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.

J.S. Leigh 9/15/99

PI - Signature Date

TABLE OF CONTENTS

INTRODUCTION

The training program in Breast Cancer Detection and Treatment continues to provide an excellent opportunity to train research specialists in techniques for clinical and technical work relating to breast cancer. This program has established solid, productive teaching relationships between highly skilled and experienced cancer specialists and qualified recipients. It has also fostered the development of diagnostic and therapeutic technology and the examination of clinical issues concerning this widespread disease.

The dual mentorship system that is in place ensures that each of the trainees in the program are assigned both a clinician and a basic scientist as his or her individual advisors. The trainees benefit enormously from this system, which provides them with two distinct and often complementary sources of insight into the progress of their work and training. Program participants are currently trained in clinical and theoretical procedures by which to detect breast cancer at early stages; they also familiarize themselves thoroughly with the current knowledge of the biology and pathology of the disease and modern therapeutic practice as part of their training. Through their clinical advisor, trainees have access to the resources necessary for clinical research, as well as to the advisor's considerable background in clinical practice and parameters. The extent to which the trainees immerse themselves in clinical research varies according to the area of specialty to which they have gravitated.

The training faculty have been selected to fill either the role of clinician or of theoretical scientist on the basis of their specialization. In our search for qualified advisor candidates, we have sought to exploit existing collaborations between clinic and laboratory in the field of breast cancer research, in an effort to provide an advisory structure conducive to the trainee's academic and professional development.

Our fundamental goal remains to develop new techniques by which to detect and to treat breast cancer, and to enhance those already existing with new knowledge and technological improvements. A significant step towards this end is naturally the thorough training of qualified specialists seeking to gain experience in the theoretical and clinical fundamentals of breast cancer research.

What follows is a brief outline of the available clinical and research techniques in which the four members of the program are being trained, supplemented by a description of the related research undertaken by the trainees in the course of this funding year. We also present the academic status and professional profile of each trainee, as well as a discussion of his or her relationship with both individual advisors and pertinent information about each. Finally, we list the events, activities, and expectations associated with the trainees' participation in the program.

BODY

Magnetic Resonance Imaging (MRI) has established itself on the forefront of medical technology as a non-invasive clinical procedure by which to obtain highly accurate metabolic and oncologic profiles of isolated tissues within the body. The research division of our laboratory dedicated to the use of MRI in the detection and treatment of breast cancer remains extraordinarily active. The group at the University of Pennsylvania has pioneered using the architectural appearance of lesions seen on breast MRI to further characterize them as benign or malignant. Although the architectural analysis does not allow complete characterizations of lesions on breast MRI, this work adds a new piece of information to assist in interpreting breast MRI. Proton spectroscopy of enhancing lesions seen on breast MRI is used to detect a compound called choline in breast lesions. Choline is commonly seen in actively growing cells, and therefore was hypothesized to be a specific marker of breast cancer. The data demonstrates that the presence of choline in enhancing lesions in the breast is almost 100% predictive of breast cancer. These findings are very significant in that they suggest that proton spectroscopy may represent an important component of the breast MRI examination. Expansion of this work into a larger set of patients is ongoing.

We have made several advances in developing techniques by which to differentiate between benign and malignant enhancing breast lesions using MRI. Such techniques would greatly improve the specificity of breast MRI techniques, given that only about 40% of breast lesions detectable by MRI constitute actual cancer. We will continue to study the kinetics of image contrast enhancement and combine this with our work on breast architectural features in order to provide an improved interpretation model for breast MRI. It is hoped that this work will eliminate the problem of detecting false positives using such a technique.

We are continuing to study the ability of MRI to determine the local extent of breast cancer. This information is essential to the planning of appropriate therapies (lumpectomy vs. quadrantectomy vs. mastectomy).

The program trainees receive comprehensive instruction in the technological principles and procedures fundamental to the research described above. In addition, the trainees are currently engaged in research projects applicable to the broader fields of oncology and pathology. These are introduced below.

Experimental Demonstration of Photon Diffusion Imaging and Diffusive Emission Tomography in Highly Scattering Systems Approximating Breast Tissue

At present there is considerable interest in the use of multiple scattered light in optical tomography, due in part to its potential applications in medicine. While X-ray CT, MRI, and PET have proven to be clinically useful, each suffers from limitations that restrict its application in the widespread screening for cancer in asymptomatic patients. Principal among these limitations are cost and the patients repeated exposure to ionizing radiation in the case of CT and PET. Optical and near-IR wavelengths, at relatively low intensity, suffer no such limitations. Spatial variations in the absorption and scattering properties of a given tissue reveal much about its metabolic state, vascularization, and structure. In addition, mapping the distribution of fluorescently tagged antibodies, in analogy to PET's use of radionuclides, may provide a means of localizing subclinical tumors with great specificity.

A fundamental problem in the reconstruction of images obtained from multiply scattered light is that of mapping variations in the scattering (diffusion) and absorption coefficients. In such highly scattering systems photons migrate in a random walk, experiencing numerous collisions along the path from source to detector. We can regard the transport of scattered light as occurring by means of diffusing waves that are described by integral equations. These integral equations are solved either numerically or by direct inversion in order to reconstruct spatial fluctuations in the absorption and diffusion coefficients of objects embedded in scattering

media. In an analogous manner, we also are able to determine spatial variations in fluorophore number densities of fluorescently labeled objects embedded in scattering media.

Our current studies have focused upon experimental validation of our numerical and analytical solutions of these integral equations. Using amplitude modulated, near-IR light sources in continuous wave mode, we record the intensity and phase of the transmitted light as a function of source/detector position. To date, we have successfully reconstructed images of phantoms whose absorption and scattering properties differ from background in a manner that approximates in situ, tumorigenic tissues. We have also incorporated fluorescently labeled probes into our phantoms and successfully reconstructed not only the object's spatially dependent absorption and scattering properties, but also the spatial distribution of its fluorophores. Numerical simulations of these experiments, incorporating results from the exact (nonperturbative) solution of the forward scattering problem, have been done to rigorously examine the effects that noise, as well as uncertainties in source/detector position and background absorption/diffusion coefficients, have on the quality of image reconstruction. Additional numerical studies have also been performed to assess the simulated data's correlation to experiment. More recently, we have conducted a series of sensitivity experiments aimed at determining the minimal fluorophore number densities needed for image reconstruction in inhomogeneously absorbing and scattering backgrounds. Our findings suggest that, with additional sources and detectors, these techniques could be of significant clinical value in the widespread screening of subclinical breast carcinoma.

Determining Heat Deposition by MRI Coils with an $Na_4HTm[DOTP]$/Agarose Phantom

The advantages of high field MR Imaging have brought with it the disadvantages of increased power delivered to MRI coils. This has challenged the MR community to develop a method to determine specific absorption rates in tissues subjected to MRI procedures. For transmit/receive surface coils, the electric field is highest at the capacitors. It is the interaction of the electric field with the tissue which theoretically causes local heating. However, it is unclear what in practice this heating might be, if at all.

We have previously characterized a temperature dependent chemical shift for ^{23}Na in $Na_4HTm[DOTP]$. This shift is very near 0.5 PPM per °C, both for a solution and in agarose. We then constructed a large agarose phantom with 40 mM $Na_4HTm[DOTP]$ and performed high power MR imaging experiments with 4 different surface coils, varying in the amount of distributed capacitance from 1 to 4 symmetrical positions. Our goal was to determine the effect of distributing capacitance on heating patterns. Phase difference maps of the phantom describe areas of local heating in the sample. In the phase difference maps, we observed areas of intense heating at the coil/phantom junction, falling off as the coil/phantom distance increases. Intense hot spot heating from the capacitors was not observed in any of the surface coils. These preliminary results suggest that heating of tissue from an MRI examination may be dominated by the inductive electric field elements and that conservative electric field heating may be negligible.

In NMR studies of breast tissues, which are located outside the body cavity, the use of surface coils provides many advantages. Surface coils not only enhance breast tissue's signal to noise ratio, but also decrease the necessary amount of RF power deposition in the body during RF pulsing. In addition, surface coils can provide easy localization of the NMR signal to breast tissue in the absence gradients or other means of localization. The localized sensitive volume of the surface coil also prevents the aliasing of signal from outside of breast into the field of view during imaging of breast or parts of the breast.

However, the B1 fields generated by the surface coils are not uniform, which results in variations in tip angles throughout the sensitive volume. For example, in spin echo imaging, this can cause severe distortions. One way to excite uniform tip angles across an imaging volume with surface coils is to use adiabatic pulses. I have been investigating the combination of adiabatic half passage and adiabatic refocusing pulses with surface coils in alleviating the distortions caused by the non-uniform B1 fields. Computer simulations of the distribution of B1

amplitudes in the sensitive volume of the surface coil are done in combination with simulations of the motions of the magnetization vectors under the adiabatic pulses at these B1 values in order to predict the resultant tip angles within the sensitive volume of a surface coil after adiabatic pulses. The shapes of both of the adiabatic pulses are numerically optimized to broaden the range of B1 in which it can still achieve a fixed tip angle. Spin echo images of phantoms are obtained using the surface coil - adiabatic pulse combination.

The STEAM pulse sequence can be used in combination with surface coils to achieve precise spatial localization while preserving the signal to noise advantage. I have shown, via phantom experiments, that precise spatial localization can be acheived using the STEAM-surface coil combination. I have also designed simple methods of calibrating the 90 degree pulses at desired locations. These have also been demonstrated to work in phantom experiments.

In summary, the surface coil and adiabatic pulse technique can be used to obtain spin echo images of the breast. The surface coil and STEAM combination can be very useful in obtaining localized spectra of any part of the breast. One obvious application is in the comparison of spectra from normal versus regions of breast suspected of tumor.

High Resolution Breast MRI

We have concentrated our efforts both on improvements of the hardware required to form magnetic resonance images and on the theory of the data acquistion process itself.

Our studies of the magnetic resonance hardware used for high resolution breast imaging have included computer modelling, prototype construction, and engineering of the final forms of both novel radiofrequency multi-coil arrays and a new design for high resolution biplanar imaging gradients. Both of these new designs improved the sensitivity and capability of the breast imaging project. The radiofrequency coil improved the overall sensitivity of the imaging process by 30% allowing higher signal-to-noise ratio images to be obtained at present resolution levels or alternately, higher resolution images to be obtained in the same period of time. The biplanar gradient design, which produced homogeneous gradients of roughly 6 gauss/cm over the breast, were designed and constructed to function with the new radiofrequency coil design in addition to allowing access to allow for the possibility of MR guided breast and localization of tumors which might otherwise be invisible to conventional mammography. Because the biplanar gradients were successfully interfaced to the clinical imaging system at the Hospital of the University of Pennsylvania with appropriate new eddy current compensation all of the standard clinical pulse sequences available could be interfaced with the enhanced capabilities of the biplanar gradients. The increased strength of the biplanar gradient design over the standard gradients available on the clincal magnetic resonance imager allows images with resolutions roughly 6 times higher than the standard images to be obtained. The smallest imaging field of view that could be obtained with the biplanar gradient set was roughly 2 centimeters. The second generation gradient design has been modified to be 20% stronger than the original design with the same high degree of homogeneity and improved acoustic noise reduction capabilities. In addition, the materials used to construct the gradients will help eliminate prior problems with heating of the local gradient set.

Theoretical studies of the magnetic resonance data acquistion process have also been ongoing with two specific goals. First, increase the inherent sensitivity of the acquisition process by manipulation of the available parameters in the pulse sequence and data acquisition. Any process which increases the inherent sensitivity of the imaging process will allow images of better quality, higher resolution, and shorter imaging times to be acquired. Second, increase the resolution of the data gathered by novel manipulation of the digitization of the data that is acquired in the imaging process. Increasing the sensitivity of the imaging process requires foreknowledge of the relaxation parameters of the tissue of interest. Once the transverse

relaxation time is known, the theoretical resolution that can be obtained is known. Knowledge of the longitudinal relaxation time provides information regarding the optimal pulse power and repetition times. Although, individually, each of these parameters points to an optimal method of data acquisition in order to maximize either resolution or sensitivity they are not all necessarily independent of one another. Once the question is framed: "How do I get an image of the highest possible resolution in the shortest period of time?" the optimal choice of pulse sequence, pulse power, repetition rate, data matrix, field-of-view, and data acquisition rate becomes a much more complicated, and clearly interdependent, optimization problem. A prescription has been formed which, when knowledge of the longitudinal and transverse relaxation times is available, will enable each of these parameters to be set in a novel optimal fashion. In addition, in order to enhance the resolution of the images obtained with the newly developed optimum prescription the digitization of the data has been altered to limit errors introduced by the limited bit resolution in the analog-to-digital converters (ADC). Since the data which reperesents the high resolution information in the image resides at the edges of the "k-space", where the peak signal levels are typically lower than at the center of k-space, the gain levels are not optimally set to accurately digitize this information. That is because the gain level for any given imaging sequence is typically set such that the highest signal level will just fill the ADC and thus be digitized to the limit of the hardware's capability. Thus, with the special capabilities of the home built spectrometer at our facility we can vary the gain level dynamically to a time resolution of 10 microseconds or better. Thus, we could vary the gain level between each acquisition point if desired. Simulations of the effects of this technique indicate that in lower level signal to noise ratio images the noise level may be significantly reduced because a large part of it is due to digitization noise. In images with higher levels of signal this effect is small. However, the regions of the image in which high fourier component information exists, mainly edges, the image quality is greatly enhanced allowing much better discrimination of edge features. Experiments applying this techniqued have been performed on biological phantoms with great success. Future applications to in-vivo imaging are soon to be performed.

Enhanced Protective Immunity by Recombinant Murine Interleukin-12 is Preceded by a Transient Suppression of Anti-Tumor Immunologic Responses

There is currently exploration into cytokine based strategies by which to induce an immunologic reaction against tumors. Such strategies are of particular interest for their potential to elicit a durable, effective response from the immune system without being excessively toxic. Among the cytokines tested, one of the most promising is interleukin 12 (IL-12). It has demonstrated consistent activity against a variety of murine tumors, be it in the form of a recombinant protein or as a cytokine secreted by tumor cells engineered for that purpose. The use of recombinant IL-12 (rIL-12) is particularly conducive to clinical application since it avoids the need for gene transfer. IL-12 by itself is effective against many tumors and, in cases where it is not, combining it with B7 co-stimulatory molecules or IL-2 has proven equally effective. The cytokine can exert effects on lymphoid and non-lymphoid cells directly or indirectly (an example of the latter is via induction of IFN-gamma); these in turn alter the host-tumor relationship favorably and in distinct ways. Such a pleiotropy of effects, however, makes it difficult to isolate the specific mechanism(s) underlying the effectiveness of IL-12 against tumors.

Our studies of rmIL-12 and its anti-tumor effects have revealed that it can synergistically induce protective immunity against poorly immunogenic SCK mammary carcinoma cells, in conjunction with the expression of B7-1 co-stimulatory molecules in tumor cells. It was our goal to determine the mechanism of rmIL-12 efficacy. Our studies primarily focused on the effect that rmIL-12 exerts on vaccination brought about by irradiated SCK tumor cells that secrete GM-CSF. Surprisingly, administering rmIL-12 ultimately ablated evidence of anti-tumor CTL activity in the spleen. It also attenuated, in direct correlation with the dosage, the secretion by splenocytes of tumor-specific cytokines. We hypothesized that the suppressive effect of rmIL-12 seen at 14 days after vaccination could have been due either to the impaired immunization or to

the effector (rejection) response. To test this later possibility directly, we chose to determine protective immunity in rmIL-12 treated animals 28 days after vaccination, at a time when mitogenic responses have returned to normal. Vaccinated mice that received rmIL-12 were much better able to reject tumor cells than vaccinated mice that had not received rmIL-12 at this later time.

From these studies, we can conclude that rIL-12 is a promising adjuvant for a tumor cell vaccine; however, its ability to suppress immunologic responses temporarily suggests the need to establish sound guidelines for the proper dosage and scheduling of the medication. While in the clinic in which our work is being done, we will need to provide careful immunologic monitoring during various protocols of rIL-12 use in order to determine whether the issues raised here are significant in human cancer therapy. By doing so, our aim is to optimize the use of this compound as an immunologic adjuvant and as an anti-tumor agent.

Hadamard Encoded Imaging and Its In vivo Applications

High resolution imaging techniques using noninvasive modalities such as magnetic resonance imaging have been pursued as in vivo cancer screening techniques in an attempt to eliminate the invasive nature of surgical biopsy. The resolution and field of view attainable with magnetic resonance imaging has been limited in the past due to aliasing of the image. We are developing a technique that uses this aliasing to produce high resolution images with larger matrix sizes than are currently available. It is performed in two dimensions, the frequency encoding and phase encoding direction, and the image is allowed to alias in both. The individual, aliased fields of view can be recovered by encoding the spatial information within the plane of the image using Hadamard methods. These images may then be tiled to obtain a composite image with high spatial resolution and a large field of view. This technique is demonstrated using two-dimensional and three-dimensional in vivo imaging of the human brain and breast.

The following is a list of trainees supported this year, including the period of their appointment and the names of their individual advisors:

Trainees	Period of Appointment	Advisors
Uma Duvvuri	9/1/97 — 8/31/98	John S. Leigh, Ph.D. Susan Orel, MD
Jeff Souris	9/1/97 — 8/31/98	Britton Chance, Ph.D. Mitchell Schnall, MD/Ph.D.
Erik Shapiro	1/1/98 — 12/31/98	Robert E. Lenkinski, Ph.D. Gilles McKenna, MD, Ph.D.

Uma Duvvuri

Uma Duvvuri is an MD/PhD student at the University of Pennsylvania Medical School. Uma was appointed as a trainee on September 1, 1997. He started in September, 1998 taking graduate level courses. Uma's scientific advisor is John S. Leigh, Ph.D., the Britton Chance professor of radiology and director of radiology research at the University of Pennsylvania. Uma attended the Seventh Annual Scientific Meeting of ISMRM where he presented two posters.

Erik Shapiro

Erik Shapiro is a graduate student in the Chemistry Graduate Group. He began his training in the program on January 1, 1998. Gilles McKenna, MD, Ph.D. serves as Erik's clinical advisor. Dr. McKenna is chairman of the Department of Radiation Oncology and his primary interests include the identification of molecular and genetic markers in tumors that indicate resistance and/or sensitivity to radio waves. His scientific advisor is Robert E. Lenkinski, Ph.D. Together, they are investigating the use of 4 different surface coils. Our goal was to determine the effect of distributing capacitance on heating patterns.

Jeffrey S. Souris

Jeffrey Souris is a graduate student in the Structural Biology and Molecular Biophysics Graduate Group. Jeff completed his fourth year in the training program on August 31, 1998. During the year he has worked with his two advisors, Drs. Britton Chance and Mitchell Schnall. Dr. Schnall is both a skilled clinician and researcher who has actively pursued the development of NMR techniques for diagnosing breast and prostate cancer. Jeff has been trained in a technique, called Photon Diffusion Imaging, that is potentially useful in gathering imaging data from any number of tissues. This technique holds great promise as a new modality in the early detection of breast cancer, one that does not pose the hazards associated with x-rays. In working with his clinical advisor Jeff has learned about the nature and pathologic parameters of breast cancer, currently available diagnostic tools, and the strengths and weaknesses of these tools in detecting breast disease in its early stages. Jeff is in the process of writing his thesis and is going to defend in October, 1999.

The following is a list of trainees supported for all years, including the period of their appointment:

Trainees	**Period of Appointment**
Jeff Souris	9/1/94 - 8/31/98
Donald Li	8/1/94 - 7/31/97
Enn-Ling Chen	9/1/94 - 8/31/97
Erik Insko	6/1/95 - 5/31/96
Holly Kurzwa	6/1/96-5/31/98
Uma Duvvuri	9/1/97 - 8/31/98
Douglas Fletcher	8/1/97 - 7/31/98
Erik Shapiro	1/1/98 - 12/31/98

KEY RESEARCH ACCOMPLISHMENTS

Photon Diffusion Imaging holds great promise as a new modality in the early detection of breast cancer, without the hazards associated with x-rays

Magnetic Resonance Imaging (MRI) provides an important new tool for the diagnosis and evaluation of breast cancer

We have constructed the second generation of a local gradient set which meets the requirements of breast imaging

To detect and characterize breast cancer with high resolution MRI

To describe architectural findings on post-contrast breast MR that are highly predictive of benign and malignant breast lesions.

REPORTABLE OUTCOMES

Enn-Ling Chen, Holly Kurzawa, and Doug Fletcher have all received their doctorate degrees in 1998. Erik Insko is currently a radiology resident in the MRI section of the Department of Radiology. Erik is a MD/PhD. Uma Duvvuri is in his fourth year of a MD/PhD program at the University of Pennsylvania. He currently received an Individual Fellowship Award from the National Institute of Mental Health.

CONCLUSIONS

We consider the process of education within the training program to be highly mutual. Trainees cull vast amounts of information about the pathology and treatment of breast cancer through discussion with their advisors and regular attendance at seminar series and conferences related to or directly dealing with the disease. In exchange, we expect trainees to disseminate their individual contributions to current knowledge via presentation of their work at conferences and conventions within the scientific community and within the larger community of persons concerned with or affected by the disease.

To be specific, we require that all trainees attend a monthly seminar series called FOCUS, which is hosted by the Group for Women's Health Research and deals with many issues facing today's breast cancer researchers. There are similar seminar series within the Department of Biochemistry and Biophysics and the Department of Cell and Molecular Biology which provide trainees with a solid grounding in the work being done in the broader fields of pathology and oncology. In addition, trainees have traveled to meetings and conferences all over the country to present their work and to elicit feedback from experts in their individual fields. Towards the end of reaching the more general scientific public, trainees have published papers and findings in widely-read scientific journals, newsletters, and brochures. These latter serve the double function of increasing awareness about the training program at the same time that they report on the work of the individual trainees.

The external advisor to our training program is Joann S. Ingwall, Ph.D. She is professor of medicine at Harvard Medical School. Dr. Ingwall's primary obligations to the program consist of offering advice and guidance to the director of the program. In addition, she reviews the progress of all present trainees and suggests possible alterations or improvements to the path of their research.

Our experience thus far with the program has been decidedly positive; we have found it to be an excellent mechanism by which to equip promising researchers with an enormous amount of clinical and technological knowledge relating to breast cancer detection and treatment. We have a strong desire to expand the program within our laboratory to accommodate yet more trainees and to expand the scope of our professional liaisons to include clinicians and research experts from an even greater geographic area.

We continue to search ardently for qualified minority and women candidates and to encourage their interest in the program. Of the eight candidates supportedd by this program, half were minority and women candidates. The program is promoted to minority candidates by a number of means. We send informational brochures to medical and engineering schools with large minority populations. We also contact persons at the University of Pennsylvania's medical school, biochemical graduate studies office, and engineering school who are qualified to refer interested candidates to us. Through these contacts, we ensure that the program is prominently advertised the minority outreach efforts undertaken by these schools. We keep our contacts informed of scientific workshops, seminars, and training sessions going on within our facility, stressing that interested minority candidates are encouraged to attend. Such events are excellent opportunities for the candidates to interact with the faculty and to be introduced to the specific work we do.

Having obtained the names of potentially eligible minority candidates, we invite them to submit their application to the program and to visit our facility to learn more about opportunities in breast cancer research and about the nature of the training program. In this way, we hope to provide as much information and encouragement as possible to minority candidates to aid them in their decision whether to apply.

PUBLICATIONS:

Papers

Coughlin C.M., Salhany K.E., Wysocka M., Aruga E., **Kurzawa H.**, Chang A.E., Hunter C.A., Fox, K.C., Trinchieri G., Lee W.M.F.: Interleukin-12 and interleukin-18 synergistically induce murine tumor regression which involves inhibition of angiogenesis. J. Clin. Inv., in press.

Reddy, R., Stolpen, A., **Insko, E.,** and Leigh, J.S. ^{17}O Decoupled ^{1}H Detection Using a Double Tuned Coil, *MRI* 14: 8 (1996).

Kurzawa H., Wysocka M., Aruga E., Chang A.E., Trinchieri G., and Lee W.M.F.: Recombinant interleukin-12 enhances cellular immune responses to vaccination only after a period of suppression. Cancer Res., **58**: 491-499.

Wysocka M., Coughlin C.M., **Kurzawa H.L.**, Trinchieri G., Eck S.L., and Lee W.M.F.: Mechanism of the induction of anti-tumor immunity by B7-1 and interleukin-12. Ann. of the New York Acad. Sci. 795: 429-33, 1996.

Duvvuri U., Reddy R., Patel S.D., Kaufman J.H, Kneeland J.B., Leigh J.S. T_{1r} Relaxation in Articular Cartilage: Effects of Enzymatic Degradation. *Magn. Reson. Med.* 38: 863-867, (1997).

Insko, E.K., Connick, T.J., and Schnall, M.D., Orel, S.G. Multicoil Array for High Resolution Imaging of the Breast. *Magnetic Resonance in Medicine* 37: 778-784 (1997).

Reddy, R., **Li, S.,** Noyszewski, E.A., Kneeland, J.B., and Leigh, J.S. In Vivo Sodium Multiple Quantum Spectroscopy of Human Articular Cartilage, *MRM* 38: 207-214 (1997).

Souris, J.S., Ishii, M., and Schotland, J.C. Experimental Demonstration of Diffusive Emission Tomography, *Optical Tomography and Spectroscopy of tTissue: Theory, Instrumentation, Models, and Human Studies II,* p. 225-231, 1997.

Wang, Z., **Li, S.,** Cohen, A., Hubbard, A.M., Moore, J., Leigh, J.S., Meyer, J.S., Haselgrove, J.C. Magnetic Resonance Measurement of Volume Magnetic Susceptibility Using A Reference in Contact---Possible Applications in Tissue Non-heme Iron Level Evaluation, Submitted to *JMRI*, (1997).

Duvvuri, U., Kaufman, J.H., Patel, S.D., Bolinger, L., Kneeland, J.B., Leigh, J.S., and Reddy, R. Sodium Multiple Quantum Spectroscopy of Articular Cartilage: Effects of Mechanical Compression. *Magnetic Resonance in Medicine. 40(3):370-5, 1998.*

Elliott, M.A., **Insko, E.K.**, Greenman, R.L., and Leigh, J.S. Improved Resolution and Signal-to-Noise Ratio in MRI via Enhanced Signal Digitization, *Jrl. of Magn. Res.* 130: 300-304, 1998.

Chen, Enn-Ling, "Nuclear Magnetic Relaxation of Water Protons in Protein Solutions and Tissue: Insights into Mechanism and Application in MRI using Low Frequency Dispersion", Doctoral Dissertation, University of Pennsylvania, 1998.

Fletcher, D.W., "Hadamard Encoded Imaging and its *In Vivo* Applications", Doctoral Dissertation, University of Pennsylvania, 1998.

Duvvuri, U., Leigh, J.S., and Reddy, R. Detection of Residual Quadrupolar Interaction in the Human Breast in vivo Using Sodium-23 Multiple Quantum Spectroscopy. *Journal of Magnetic Resonance Imaging. 9(3):391-4, 1999.*

Shapiro, E.M., Borthakur, A., Reddy, R.R., Bansal, N, Leigh, J.S., and Reddy, R., Temperature Dependent Chemical Shift and Relaxation Times of ^{23}Na in $Na_4HTm[DOTP]$, *J. Mag. Res. (in press).*

ABSTRACTS

Insko, E.K., and Leigh, J.S. Inductance Optimized Linear RF Coil, Soc. of Magn. Res., Second Annual Meeting, p. 1096 (1994).

Insko, E.K., and Leigh, J.S. Biplanar Gradients for High Resolution MRI of the Breast, Soc. of Magn. Res., Second Annual Meeting, p. 1072 (1994).

Kim (Chen), E.L., Kim, R. J., and Leigh, J. S. The Relationship between BSA Cross-link Density and Water T1p Dispersion: Mechanisms of T1p Dispersion in Tissue" Soc. of Magn. Res., Third Scientific Meeting, p. 1031 (1995).

Fletcher, D.W., Haselgrove, J.C., and Bolinger, L. High Resolution Imaging Using NxN Hadamard Encoding, Soc. of Magn. Res., Fourth Annual Meeting, p. 1531 (1996).

Li, S., Reddy, R., **Insko, E.K.**, and Leigh, J.S. The Observation of Sodium Signal Change upon Visual Stimulation, Soc. of Magn. Res., Fourth Scientific Meeting, p. 378 (1996).

Chen, E.L., Leigh, J.S., and Kim, R.J. Importance of Protein Structure and Chemical Exchange in T1_Water Relaxation, V Annual Meeting of ISMRM, p. 1547, 1997.

Chen, E.L., Leigh, J.S., and Kim, R.J. Water T1r Relaxation Mechanisms: The Role of Spin Exchange Between Macromolecules and Water, V Annual Meeting of ISMRM, p. 1548, 1997.

Chen, E.L., Leigh, J.S., and Kim, R.J. Water T1_ and T1 Relaxation in Protein Solutions and Tissue: A Link Between Low and High Frequency Water Dynamics? V Annual Meeting of ISMRM, p. 1566, 1997.

Duvvuri, U., Noyszewski, Reddy, R., and Leigh, J.S., *In Vivo* Sodium Multiple Quantum Spectroscopy of Human Breast, *V Annual Meeting of ISMRM*, p. 1356, 1997.

Fletcher, D.W., Haselgrove, J.C., Bolinger, L. Increased Image Resolution using Longitudinal Hadamard Encoding. *The 38th Experimental NMR Conference,* p. 5, (1997).

Kurzawa, H. Recombinant Interleukin-12 Enhancement of Tumor Vaccine-Induced Protection is Preceded by a Period of Impairment, *Gordon Research Conference on Cancer*, 1997.

Kurzawa, H. Young Investigators Panel, Department of Defense Breast Cancer Research Program Meeting: An Era of Hope. Washington DC, 1997.

Kurzawa, H., Wysocka, M., Aruga, E., Chang, A., Trinchieri, G. and Lee, W.M.F. Development of a Breast Cancer Vaccine Using Irradiated Tumor Cells and Interleukin-12, The Department of Defense Breast Cancer Research Program Meeting: An Era of Hope. Washington DC, 1997.

Souris, J., Ishii, m., Leigh, J.S. and Schotland, J.C. Experimental Demonstration of Photon Diffusion Imaging and Diffusive Emission Tomography in Highly Scattering Systems Approximating Breast Tissue, The Department of Defense Breast Cancer Research Program Meeting: An Era of Hope. Washington DC, 1997.

Charagundla, S., Noyszewski, E.A., Dandora, R., **Duvvuri, U.,** Stolpen, A.H., Leigh, J.S. and Reddy, R. Measurement of ^{17}O Using a Surface Coil: STEAM Decoupling, Sixth Annual Scientific Meeting of ISMRM, p. 1896, (1998).

Dandora, R., **Shapiro, E.,** Borthakur, A., **Insko, E.K.**, Kneeland, J.B., Noyszewski, E.A., Lenkinski, R.E., and Leigh, J.S. *In vivo* Sodium MRI of Human Cartilage at 4.0T, Workshop on Magnetic Resonance of Connective Tissues and Biomaterials, ISMRM, p. 39, (1998).

Dandora, R., **Shapiro, E.M.,** Borthakur, A., Noyszewski, E.A., Kneeland, J.B., Leigh, J.S. and Reddy, R. ^{23}Na Imaging of Articular Cartilage at 4T, XVIIIth International Conference on Magnetic Resonance in Biological Systems, p. 96, (1998).

Duvvuri, U., Borthakur, A., Dandora, R., Dodge, G., Leigh, J.S., and Reddy, R. The Impact of Proteoglycan Degradation on the Residual Quadrupolar Interaction in Articular Cartilage. Sixth Annual Scientific Meeting of ISMRM, p. 1936, (1998).

Duvvuri, U., Noyszewski, E.A., Dimitrov, I., Dandora, R., Insko, E., Leigh, J.S., and Reddy, R. Sodium Imaging of Skeletal Muscle at 4.0T, Sixth Annual Scientific Meeting of ISMRM, p. 1071, (1998).

Fletcher, D.W., Haselgrove, J.C., Bolinger, L. Increased Image Resolution using Longitudinal Hadamard Encoding. The 38th Experimental NMR Conference, p. 56, (1997).

Shapiro, E.M., Borthakur, A., Dandora, R., Kriss, A., Leigh, J.S., and Reddy, R. Sodium Quantitation and Visibility in Bovine Articular Cartilage at 4.0T, Workshop on Magnetic Resonance of Connective Tissues and Biomaterials, ISMRM, p. 38, (1998).

Shapiro, E.M., Borthakur, A., Dandora, R., Kriss, A., Leigh, J.S. and Reddy, R. Sodium Quantitation and Visibility of Intact Bovine and Human Articular Cartilage, XVIIIth International Conference on Magnetic Resonance in Biological Systems, p. 95, (1998).

Borthakur, A., **Shapiro, E.M., Duvvuri, U.,** Beers, J., and Reddy, R. Comparison of Sodiumand Proton MRI in the Assessment of Proteoglycan Depletion in Cartilage, Workshop on Magnetic Resonance and Optical Imaging Techniques for Biomedical Applications, p. 37,1999.

Borthakur, A., **Shapiro, E.M.**, Dandora, R., and Reddy, R. Removal of Synovial Fluid Signal During Sodium MRI of Patella Using an IR-Prepared GRE Imaging Sequence, Proc. 40thExperimental NMR Conference, p. 151, 1999.

Charagundla, S.R., Rizi, R., Stolpen, A.H., **Duvvuri, U.,** Leigh, J.S., and Reddy, R. ^{17}ODetection with Single-Shot ^{1}H $T_{1\rho}$-Dispersion MRI, Workshop on Magnetic Resonanceand Optical Imaging Techniques for Biomedical Applications, p. 38, 1999.

Charagundla, S.R., **Duvvuri, U.,** Rizi, R., Poptani, H., Stolpen, A.H., Leigh, J.S., and Reddy, R. Dynamic ^{17}O Imaging with Fast $T_{1\rho}$ Dispersion MRI, Seventh Scientific Meeting of ISMRM, p. 2106, 1999.

Dandora, R., **Shapiro, E.M.,** Borthakur, A., Noyszewski, E.A., Kneeland, J.B., Leigh, J.S., and Reddy, R. ^{23}Na Imaging of Articular Cartilage at 4T, *XVIIIth International Conference on Magnetic Resonance in Biological Systems,* (1998).

Duvvuri, U., Borthakur, A., Dandora, R., Dodge, G., Leigh, J.S., and Reddy, R. Impact of Proteoglycan Degradation on the Residual Quadrupolar Interaction in Articular Cartilage, Proc. Int. Soc. Magn Reson Med., p. 1936, (1998).

Duvvuri, U., Walter, G.A., Reddy, R., Sweeney, H.L., and Leigh, J.S. Sodium MQ Measurements of MDX Mice, Workshop on Magnetic Resonance and Optical ImagingTechniques for Biomedical Applications, p. 40, 1999.

Kaufman, J.H, Reddy, R.R., **Duvvuri, U**., and Reddy, R. Interleaved ^{1}H and ^{23}Na Imaging of Articular Cartilage During Compression, Workshop on Magnetic Resonance and Optical Imaging Techniques for Biomedical Applications, p. 42, 1999.

Reddy, R., Borthakur, A., **Shapiro, E.,** Kaufman, J.H., Reddy, R.R., Duvvuri, U.,Noyszewski, E.A., and Kneeland, J.B. Functional MRI of Cartilage, Workshop on Magnetic Resonance and Optical Imaging Techniques for Biomedical Applications, p. 10, 1999.

Shapiro, E.M., Bansal, N, Reddy, R.R.,Borthakur, A., Leigh, J.S., and Reddy, R.Visualization of RF Heating Using a Na_4HTm[DOTP] Doped Agarose Phantom, Seventh Scientific Meeting of ISMRM, p. 420, 1999.